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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,918	09/24/2002	Joseph P. Noel	SALK2370-2	1639

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EXAMINER	
NASHED, NASHAAT T	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,918	NOEL ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *2-5,7-16,18-21 and 27-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,17 and 22-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/7/03 & 7/21/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 1-39 are pending.

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions, which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.
Group I, claim(s) 1-6 and 17-27, drawn to polyketide synthase and crystal thereof.

Group II, claim(s) 7-11, drawn to nucleic acid sequence encoding polyketide synthase.

Group III, claim(s) 12-16, drawn to method of predicting the activity/or substrate specificity of a polyketide synthase by a modeling method.

Group IV, claim(s) 28-37, drawn to method of identifying inhibitor of polyketide synthase.

Group V, claim(s) 38 and 39, drawn to a computer program containing the atomiuc coordinates.

The inventions listed as Groups I-V do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The special technical feature of the invention of Group I is the polyketide synthase, which is known in the prior art (see Jez *et al.* 1999) and is not the contribution of the inventor of the instant application, whereas as that of invention II is the nucleic acid encoding the polyketide synthase. The special technical feature of invention III, IV, and V are the modeling algorithm, the algorithm by which an inhibitor can be identified, and computer respectively. Thus, inventions I-V are not so linked as to form a single general inventive concept under PCT Rule 13.1.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows: the amino acid located at position 164 is alanine or serine; the amino acid located at position 303 is alanine, asparagine, glutnmine, mqpartic acid, or threonine; the amino acid located at position 336 is a lysine, alanine, aspartic acid, glutnmine, or histidine; the amino acid located at position 336 is lysine, alanine, aspartic acid, glutamine or histidine; the amino acid located at position 215 is

serine, tyrosine, or tryptophan; 1BI5; 1BQ6; 1CML; 1CHW; 1CGK; 1CGZ; 1D6F; 1D61; and 1D6H.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

The claims are deemed to correspond to the species listed above in the following manner: 2-6, 8-11, 13, 14, 18-21, 26, 27, 31, 32, 36, 37, 39.

The following claim(s) are generic: 1, 7, 12, 13, 15, 16, 17, 22-25, 28-30, 33-35, and 38.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: The different polyketide synthase are independent chemical compounds having different function and as such require separate searches in the patent and non-patent literature.

During a telephone conversation with Stephen Reiter on April 5, 2005 a provisional election was made with traverse traverse to prosecute the invention of Group I, claims 1-6 and 17-27. He further elected the first species of claim 6, i.e., 1BI5 which is presumed to be the wild-type naringene-chalcone synthase from *Medicago sativa* (alfalfa) and form the trigonal crystal in space group $P3_221$ containing 3-sulfinoalanine. Affirmation of this election must be made by applicant in replying to this Office action. Claims 7-16 and 28-39 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Claims 1, 6, 17, and 22-26 are under consideration.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. The atomic coordinates in Table 3 represents the disclosure of an amino acid sequence, which has to be identified by a sequence identification number. Also, Table 1 contains a list of amino acid residues, which has to be identified by amino acid identification number. Through out the specification, there are many cited specific amino acid residues, which are not associated with a sequence identification number, see for example Table 1, and pages 178-180, 185, and 192. Applicants must perfect their compliance with the sequence rules.

The use of the trademark names has been noted in this application, see for example QuikChange at page 175, line 6. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, see for example page 9, line 14; page 16, lines 10, 21, and 26; and page 18, line 26. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The attempt to incorporate subject matter into this application by reference to accession numbers in a Protein Data Bank is ineffective because MPEP section 608.01 (P) states:

> "An application for a patent when filed may incorporate "essential material" by reference to (1) a U.S. patent, (2) a U.S. patent application publication, or (3) a pending U.S. application, subject to the conditions set forth below. "Essential material" is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112). In any application which is to issue as a U.S. patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, (2) non-patent publications, (3) a U.S. patent or application which itself incorporates "essential material" by reference, or (4) a foreign application."

The incorporation by reference to Protein Data Bank accession numbers at page 9, lines 5-14 is improper because the material incorporated by reference describe the invention of claim 6. The database is not a US patent, patent application or a published patent application.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Three-Dimensional Structure of Plant Chalcone Synthase.

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 17, and 22-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, and 17 are directed to all possible polyketide synthases from any biological source, which comprises an active site comprising 14 active site α-carbons having the atomic coordinates in Table 1. Also, claims 22-26 are directed to any crystal form of any chalcone synthase from any biological source and its mutant. The specification, however, only provides two representative species from these polypeptides and crystals from *M. sativa* (SEQ ID NO: 1) and *Pinus strubus* encompassed by these claims. It should be noted that the two crystals exemplified in the specification are obtained under different crystallization conditions, and that the two crystals obtained in two different space groups. There is no disclosure of any particular structure to function/activity relationship in the two disclosed species. Also, the specification fails to describe additional representative species of these polyketide synthases or chalcone synthesases by any identifying structural characteristics or properties other than the atomic coordinates of the 14 α-carbons, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Claims 1, 17, and 22-26 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are broader than the enablement provided by the disclosure with regard to all possible polyketide synthases having an active site comprising 14 α-carbons having the atomic coordinates listed in Table 1 and their mutants, and crystals thereof. Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of claim 1 encompasses any polyketide synthase from any biological source having an active site comprising 14 α-carbons having the atomic coordinates listed in Table 1 and their mutants, and crystals thereof, in particular, any chalcone synthase. The specification provides guidance and examples in the form of an assay to prepare and purify the polypetide of, presumably, the chalcone synthase SEQ ID NO: 1, crystallize said polypeptide under specific crystallization conditions to

produce a trigonal crystal in space group $P3_221$ (see example starting at page 175). Also, the specification at page 186 describes the expression of *P. strubus* stilbene synthase in *E. coli* and crystallization of the stilbene synthase under the specific crystallization conditions described at page 186 to produce an orthorhombic crystal in space group C222. While molecular biological techniques and genetic manipulation to make any polypeptide are known in the prior art and the skill of the artisan are well developed, knowledge regarding all possible nucleic and amino acid sequences of polyketide synthases or chalcone synthases from any biological sources, and their enzymatically active mutants, as well as methods of obtaining crystals thereof and their complexes is lacking. It is well established in the art that obtaining a protein and its complexes in a crystal form crystallizing is highly unpredictable. The skilled artesian would be expected to screen large number of crystallization conditions, which may include screening variety of conditions in space, a micro gravity environment. A protein which may crystallize under specific crystallization conditions, it's mutants may or may not crystallize under the same conditions. In many cases, a protein that can't be crystallized, one of its specific mutants might be crystallizable. Even if a crystal is obtained, it may or may not be suitable for structure determination by X-ray crystallography. It should be noted that the chalcone synthase (~400 amino acid resides) is relatively small protein when compared to polyketide synthase type-I required for the biosynthesis of macrolids such as erythromycin (3000-10,000 amino acid residues). Clearly, neither the specification nor the prior art have enable any crystals of any kind for type-I polyketide synthase. Thus, searching for a gene encoding a polyketide/chalcone synthase from any biological source, and/or a method to purify said synthase from its biological source, as well as crystallization conditions to crystallize the synthase and its complexes, which would produce a suitable crystal for structure determination by X-ray crystallography is well outside the realm of routine experimentation and predictability in the art of success in is extremely low. The amount of experimentation to identify a gene encoding a polyketide/chalcone synthase from any biological source, or their cystallizable mutants, and identify a crystal suitable structure determination X-ray crystallography is enormous. Since routine experimentation in the art does not include screening large number of gene, cDNA or man-made mutant libraries to identify said synthase gene, or search for a purification method of said synthase as well as a search for crystallization conditions or mutants, which can be crystallized where the expectation of obtaining the desired crystal is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the gene encoding said synthase, the amino acid sequences of the chalcone/polyketide synthase, and identify a crystallization conditions that produce a crystal suitable for structure determination by X-ray crystallography. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1, 6, 17, 22, and 26 are rejected under 35 U.S.C. ∋ 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

(a) The phrases "PDB Accession Nos: 1BI5" in claim 6 renders the claims indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. As indicated above, the incorporation by reference of "PDB Accession Nos: 1BI5" is improper, and therefore the term is unclear.

(b) The result in Table 1 contains amino acid residues from a specific amino acid sequence not identified by a sequence identification number, which renders claim 1 indefinite and confusing. For examination purposes only, it is assumed that the applicant is referring to residues from SEQ ID NO: 1.

(c) Claim 22 ends with two periods, which renders the claim in complete.

(d) The clause "the chalcone synthase is selected from the group consisting of chalcone....." in claim 26 renders the claims indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. An enzyme named chalcone synthase should produce chalcone as a product. Thus, chalcone, naringgenin, resveratrol and cerulenin can be possibly a substrate for a chalcone synthase. For examination purposes only, the substrate for chalcone synthase is malonylCoA.

(d) Claims 17 is included in this rejection because they are dependent on rejected claims and do not correct the deficiencies of the claim from which they depend.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 and 6 are rejected under 35 U.S.C. 102(a) as being anticipated by Protein Data Bank Accession number 1BI5 (IDS reference, released to the public June 22, 1999).

The accession number teach a chalcone synthase from *M. sativa* and its three dimensional structure, see the entire document.

Claim 1 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Junghans *et al.* (IDS reference, Plant Mol. Biol. 22, 239-253, 1993).

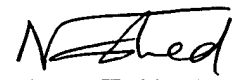
Junghans *et al.* teach five genes from *M. sativa* L. encoding chalcone synthase, see abstract. They report the nucleic and amino acid sequences for the five genes in Figures 1 and 3, respectively. The five-nucleic and amino acid sequences are highly homologous (>90%). The amino acid sequence of SEQ ID NO: 1 is that taught by Junghans *et al.* as CHS2 in figure 2 wherein X in SEQ ISD NO: 1 is Cys residue. The amino acid sequence disclosed in the protein data bank accession number 1BI5 appears to be identical to that of CHS2 disclosed by Junghans *et al.* The five chalcone synthases taught by Junghans *et al.* must have a homologous structure because of their highly homologous sequences. Thus, they all must have the same active site, and their active site residues are identifiable by the atomic coordinates in Table 1.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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